Remarks

Claims 36, 39, 46-49 and 61-65 are currently pending. Claims 47, 62 and 64 have been canceled. Claims 36, 61, and 65 have been amended. New claims 71-80 have been added. Support for the claim amendments and new claims may be found throughout the specification, including the claims as originally filed. In particular, support for "at least about 95% or 98% identical" may be found, e.g., at page 20, lines 25-27, as well as page 9, lines 24-25 (support for homology to a portion of an F-box containing protein). Support for "mammalian cell" may be found, e.g., at page 11, line 19. Support for "a nucleic acid that hybridizes under stringent hybridization conditions including a wash step at 65 °C" may be found, e.g., at page 9, lines 1-2, and page 29, line 18. "Support for "human cell" and "murine cell" may be found, e.g., at page 118, lines 14 and 15. No new matter has been added.

Cancellation and/or amendments of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. Cancellation and/or amendments to the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in any way. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Submitted herewith is a substitute Sequence Listing that includes new sequences SEQ ID NOs: 48 and 49. SEQ ID NO: 49 corresponds to amino acids 148-192 of SEQ ID NO: 4. Support for this amino acid sequence is provided, e.g., at page 30, line 10, of the specification. SEQ ID NO: 48 consists of the nucleotide sequence of SEQ ID NO: 3 that encodes SEQ ID NO: 49, i.e., nucleotides 511-645 of SEQ ID NO: 3. Support for this sequence can be found, e.g., in SEQ ID NO: 3. The specification has been amended at page 30, line 10, to refer to the new SEQ ID NOs. No new matter has been added.

Claim objections

Claim 64 has been objected to under 37 C.F.R. 1.75 as being a substantial duplicate of claim 63. Claim 64 has been canceled. Reconsideration and withdrawal of this objection is respectfully requested.

Rejection of claims 36, 39, 46-49, and 61-65 under 35 U.S.C. § 112, first paragraph (written description)

Claims 36, 39, 46-49, and 61-65 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner indicates that the "recitation of the genus fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the specifies within the genus." Applicants respectfully traverse this rejection. However, merely, for expediting prosecution of the application, the claims have been amended, and as amended, are believed to render this rejection moot.

Thus reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 36, 39, 46-49, and 61-65 under 35 U.S.C. § 112, first paragraph (enablement)

Claims 36, 39, 46-49, and 61-65 were rejected under 35 U.S.C. § 112, first paragraph,

> because the specification, while being enabling for a method for targeting a target polypeptides using a hybrid polypeptide comprising F-box protein of SEQ ID NO: 4 or its fragment consisting of residues 148-192 of SEQ ID NO: 4 and a target polypeptide interaction domain in human cells, does not reasonably provide enablement for a method of use of said hybrid polypeptide in any eukaryotic cell or its functional homolog having no known identity to residues 148-192 of SEQ ID NO: 4 in any eukaryotic cell, including human cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.
>
> Applicants respectfully traverse this rejection.

Regarding the use of functional homologs having no known identity to residues 148-192 of SEQ ID NO: 4, Applicants respectfully submit that no structural similarity between F boxes is required: the F box merely has to interact with the Skp1 subunit of SCF ubiquitin ligase complex. Numerous F boxes appear to have very different amino acid sequences from each other, yet they are all able to be degraded by the SCF ubiquitin ligase complex. For instance,

there is less than 22% similarity between yeast Cdc4 and human βTrCP. However, when fused to the E7N targeting peptide, both F box proteins efficiently targeted the retinoblastoma protein for degradation Zhou et al. (2000) *Mol. Cell* 6: 751-756. Zhang et al. (2003) *Proc. Natl. Acad. Sci. USA* 100, 14127-14132.) However, merely for expediting prosecution of this application, the claims have been amended, and as amended, they encompass structural homologs of an F-box consisting of residues 148-192 of SEQ ID NO: 4. Thus, the claim amendments are believed to render this aspect of the rejection moot.

Regarding targeting proteins in cells other than human cells, Applicants respectfully submit that hybrid proteins comprising an F box from one species are expected to target the degradation of target proteins in cells of a different species. This is possible because SCF ubiquitin ligase complexes, and in particular Skp1 proteins, are very well conserved across species (see, e.g., Bai et al. (1996) *Cell* 86(2):263-74 and Schulman et al. (2000) *Nature* 408(6810):381-6). In view of this strong conservation of Skp1 proteins, both at the sequence and structural levels, F boxes from one species are expected to interact with Skp1 proteins of SCF ubiquitin ligase complexes of other species, resulting in their degradation.

In particular, it has been shown that a fusion protein comprising the F box from the human βTrCP can target the degradation of a target protein in murine cells (Cohen et al. (2004) BMC Developmental Biol. 4:4).

In applying the Wands factors, it is evident from the above discussion that the level of skill in this art was very high at the time the application was filed, and the experimental techniques needed to practice the invention were well known and exemplified in the specification as filed. Accordingly, Applicants respectfully submit that armed with the teachings of the specification and the contemporary knowledge in the art, the skilled artisan would be able to practice the claimed methods without further undue experimentation.

The Examiner's specific arguments are believed to be addressed within the above paragraphs, as well as in the Applicant's previous responses. Thus, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claims 36, 39, 46-49 and 61-64 under 35 U.S.C. § 112, second paragraph

Claims 36, 39, 46-49 and 61-64 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

Claim 36 has been rejected, allegedly because the phrase "F-box consisting of an amino acid sequence that is encoded by the nucleotide sequence in SEQ ID NO: 3 that encodes amino acids 148-192 of SEQ ID NO: 4" is confusing. Claim 36 has been amended, and as such is believed to render this rejection moot.

Regarding claim 49, the Examiner indicates that "[w]hile some polypeptides such as IkB or β-catenin can be found in Registry or GenBank database, for example, others can not," and that "[t]hus, it is unclear which polypeptide sequences are encompassed by the recited terms." Applicants respectfully submit that "Sic1p" is a Cdk inhibitor, which is described, e.g., in Bai et al. Cell. 1996;86(2):263-74 and has, e.g., GenBank Accession numbers AAB67583 and CAA97638. "Cln2p" is a G1 cyclin, which is described, e.g., in Deshaies et al. EMBO J. 1995;14(2):303-12, and has, e.g., GenBank Accession numbers AAA65725 and CAA97982; and that "E2" refers to the papillomavirus E2 protein, as further described at pages 137-138 of the specification.

The Examiner further indicates that "it is unclear why some polypeptides contain 'p' while others such as IkB, E2 or β-catenin do not." The literature indicates that the "p" merely refers to "protein" and that "Sic1p" is the same as "Sic1" and "Cln2p" is the same as "Cln2."

Claim 61 has been rejected as being confusing for reciting "further comprising a WD domain." The claim has been amended, and as such, is believed to render this rejection moot.

Thus, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of Claims 36, 39, 46-49, 61 and 65 under 35 U.S.C. § 102(a)

Claims 36, 39, 46-49, 61 and 65 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kumar et al. (PNAS (March 1998) 95:2417). The Examiner asserts that "Kumar et al. teach a method of targeting a polypeptide comprising [an] F-box and a target interaction domain for proteolysis in a eukaryotic cell. Applicants respectfully disagree.

Kumar et al. fail to teach each and every claim limitation of the claims. In particular, Kumar et al. does not teach an F-box comprising an amino acid sequence that is encoded by a nucleotide sequence that is at least about 95% identical to SEQ ID NO: 49, which corresponds to the F-box of βTrCP. Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

If any additional fees are due, the Commissioner is hereby authorized to charge any deficiencies to Deposit Account Number **06-1448, Reference HMV-043.01**.

Respectfully submitted,

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